REMARKS

Claims 1-73 are currently pending in the application. Claims 74-75 are withdrawn as being drawn to non-elected subject matter. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s). No new matter is added.

Rejection of Claims 1, 2, 5, 10, 12, 18-19, 22, 27, 34-35, 38 and 43 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 1, 2, 5, 10, 12, 18-19, 22, 27, 34-35, 38 and 43 under 35 U.S.C. §102(b) as being anticipated by Myakishev *et al.* (*Genome Research* 2001 11: 163-169).

Applicant respectfully traverses this rejection under 35 U.S.C. §102 and requests reconsideration. As the Examiner is well aware, for a prior art reference to anticipate a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Claims 1, 18 and 34, and dependent claims 2, 5, 10, 12, 19, 22, 27, 35, 38 and 43, are directed to genotyping methods that involve, among other elements, subjecting to an amplification regimen a population of primer extension products generated from a nucleic acid sample, wherein said amplification regimen is performed using an upstream amplification primer and ***a set of distinguishably labeled downstream amplification primers***.

Myakishev *et al.* teaches fluorescent detection of SNPs using a combination of target specific primers and ***universal*** fluorescently labeled primers, which are used for amplification purposes as ***upstream*** primers (refer to Figure 2 of Myakishev *et al*). The Myakishev *et al.* reference fails to teach or suggest a process that employs ***a set of distinguishably labeled downstream amplification primers***, as is required by the present claims.

Moreover, the genotyping method described in Myakishev *et al.* relies upon an increase in fluorescent signal due to the uncoupling of fluorescent probe from a quencher attached to the primer. Thus, the Myakishev *et al.* reference fails to teach or suggest a method such as that presently claimed, in which there is no requirement for a quencher in the primer sequence.

Furthermore, the Myakishev *et al.* reference does not teach or suggest the separation of amplified species by size or charge (and specifically states that the distance between primers is not critical), as is required by instant claims 3, 6, 20, 36, 52 and claims that depend therefrom.

Therefore, for at least the reasons set forth above, Applicant submits that the Myakishev *et al.* reference does not anticipate the claimed invention. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Rejection of Claims 3-4, 9, 20-21, 26, 36, 37 and 42 Under 35 U.S.C. §103(a)

Claims 3-4, 9, 20-21, 26, 36, 37 and 42 are rejected as being unpatentable over Myakishev *et al.* in view of Piggee *et al.* (1997, *J. Chromatogr. A.*, 781: 367-375).

Applicant respectfully traverses on the grounds that the combination of references does not present a *prima facie* case of obviousness. As the Examiner is well aware, to establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "***[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure***" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. *See, e.g., Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985). Finally, ***the prior art reference (or references when combined) must teach or suggest all of the claim limitations*** (M.P.E.P. 2143).

As discussed above, Myakishev *et al.* does not teach or suggest a genotyping method that requires ***a set of distinguishably labeled downstream amplification primers***.

Applicant respectfully submits that the combination of teachings also does not arrive at the claimed invention. Specifically, the Piggee *et al.* reference teaches a genotyping process that employs ***single base extension (SBE)*** of a primer ***added to a previously amplified PCR product***. Thus, the methods of Piggee *et al.* require purification of amplified PCR product to completely eliminate primers and nucleotides used for PCR amplification prior to single nucleotide

extension. Neither Myakishev *et al.* nor Piggee *et al.* provides any suggestion or guidance that the disclosed genotyping methods might be combined. In fact, were one of skill in the art to attempt to combine the two different processes of Myakishev *et al.* and Piggee *et al.*, the SNP specificity encoded by the specific element in the 5'-part of the sequence, as taught in the Myakishev *et al.* reference, would be completely lost *via* use of a specific element located at the 3'-end of the extendable primer, as taught by Piggee *et al.* That is, Piggee *et al.* teaches single nucleotide extension by one fluorescently labeled dideoxy terminator complementary to the SNP variant, but Myakishev *et al.* requires polymerization to process through the SNP site from the reverse primer in order to open up the hairpin tag probe of the forward primer to generate a signal. Not only is the tagged primer of Myakishev *et al.* not necessary in the Piggee *et al.* method, the Myakishev *et al.* method ***will not work*** if dideoxy terminator nucleotides are used because the quenched hairpin probe of the forward primer will not be opened and unquenched by extension of the reverse strand. Thus, these methods are not combinable as suggested in the Office Action. Accordingly, Applicant respectfully submits that the Examiner has failed to point to any teaching in either Myakishev *et al.* or Piggee *et al.* that would provide one of ordinary skill in the art with both the required suggestion and expectation of success to make the presently claimed invention. Thus, the Examiner has failed to establish a *prima facie* case of obviousness.

Moreover, the Piggee *et al.* reference does not make up for the deficiencies of the primary reference of Myakishev *et al.* Specifically, the Piggee *et al.* reference teaches SBE techniques that employ labeled dideoxy chain terminator nucleotides. The Piggee *et al.* reference does not teach or suggest a genotyping method that requires ***a set of distinguishably labeled downstream amplification primers***, as is required by the claimed invention. Accordingly, the combination of Myakishev *et al.* and Piggee *et al.* references fails to teach or suggest all limitations of the presently claimed invention.

Because the combination of Myakishev *et al.* and Piggee *et al.* does not arrive at the claimed invention, a *prima facie* case of obviousness over the claims has not been established. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection of claims 3-4, 9, 20-21, 26, 36, 37 and 42 under 35 U.S.C. §103(a).

The Examiner has also rejected claims 6-8, 23-25 and 39-41 as being unpatentable over Myakishev *et al.*, in view of Weisner *et al.* (*Biochemical and Biophysical Research*

Communications 1992 183(2): 553-59), and further in view of Piggee *et al.* Applicants respectfully traverse on the grounds that the Weisner *et al.* reference relied upon by the Examiner fails to make up for the above-stated deficiencies in the Myakishev *et al.* and Piggee *et al.* references. Specifically, the Weisner *et al.* reference discloses a sampling method for determining PCR product accumulation. The Weisner *et al.* reference still does not provide any teaching that would provide one of ordinary skill in the art with both the required suggestion and expectation of success to make the presently claimed invention, nor does the Weisner *et al.* reference teach or suggest a genotyping method that requires ***a set of distinguishably labeled downstream amplification primers***, as is required by the presently claimed invention.

Based on all of the above, Applicants respectfully submit that none of the cited references of Myakishev *et al.*, Piggee *et al.*, and Weisner *et al.*, alone or in combination, teaches or suggests a genotyping method comprising, among other elements, subjecting to an amplification regimen a population of primer extension products generated from a nucleic acid sample, wherein said amplification regimen is performed using an upstream amplification primer and ***a set of distinguishably labeled downstream amplification primers***, as is presently claimed.

Accordingly, Myakishev *et al.*, Piggee *et al.*, and Weisner *et al.* fail to teach or suggest the claimed invention and, thus, Applicants respectfully request reconsideration and withdrawal of the above rejections of claims 6-8, 23-25 and 39-41 under 35 U.S.C. §103(a).

The Examiner has further rejected claims 11, 13-17, 28-33, 44-52, 54, 58-64, 66 and 70-73 as being unpatentable over Myakishev *et al.*, in view of Nolan *et al.* (U.S. Patent No. 6,287,766).

As discussed above, Myakishev *et al.* does not teach or suggest a genotyping method that requires ***a set of distinguishably labeled downstream amplification primers***.

Applicant respectfully submits that the Nolan *et al.* reference does not make up for the deficiencies of the primary reference of Myakishev *et al.* Specifically, Nolan *et al.* teaches a method of genotyping using primer extension or ligation of labeled primers on the surface of microbeads that is followed by detection using flow cytometry. However, Nolan *et al.* also fails to teach or suggest a genotyping method that requires ***a set of distinguishably labeled downstream amplification primers***, as is required by the claimed invention. Accordingly, the

combination of Myakishev *et al.* and Nolan *et al.* references fails to teach or suggest all limitations of the presently claimed invention.

Because the combination of Myakishev *et al.* and Nolan *et al.* does not arrive at the claimed invention, a *prima facie* case of obviousness over the claims has not been established. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection of claims 11, 13-17, 28-33, 44-52, 54, 58-64, 66 and 70-73 under 35 U.S.C. §103(a).

The Examiner has additionally rejected claims 53, 57, 65 and 69 as being unpatentable over Myakishev *et al.* in view of Nolan *et al.* and further in view of Piggee *et al.*

As discussed above, the combination of Myakishev *et al.* and Nolan *et al.* references fails to teach or suggest a genotyping method that requires ***a set of distinguishably labeled downstream amplification primers***, as is required by the claimed invention. As also discussed above, the Piggee *et al.* reference does not make up for these deficiencies of the Myakishev *et al.* and Nolan *et al.* references. Specifically, the Piggee *et al.* reference does not teach or suggest a genotyping method that requires ***a set of distinguishably labeled downstream amplification primers***, as is required by the claimed invention.

Based on all of the above, Applicant respectfully submits that none of the cited references of Myakishev *et al.*, Nolan *et al.*, and Piggee *et al.*, alone or in combination, teaches or suggests a genotyping method comprising, among other elements, subjecting to an amplification regimen a population of primer extension products generated from a nucleic acid sample, wherein said amplification regimen is performed using an upstream amplification primer and ***a set of distinguishably labeled downstream amplification primers***, as is presently claimed.

Accordingly, Myakishev *et al.*, Nolan *et al.*, and Piggee *et al.* fail to teach or suggest the claimed invention and, thus, Applicants respectfully request reconsideration and withdrawal of the above rejections of claims 53, 57, 65 and 69 under 35 U.S.C. §103(a).

The Examiner has also rejected claims 55, 56, 67 and 68 as being unpatentable over Myakishev *et al.* in view of Nolan *et al.* and further in view of Weisner *et al.*

As discussed above, the combination of Myakishev *et al.* and Nolan *et al.* references fails to teach or suggest a genotyping method that requires ***a set of distinguishably labeled downstream amplification primers***, as is required by the claimed invention. As also discussed

above, the Weisner *et al.* reference does not make up for these deficiencies of the Myakishev *et al.* and Nolan *et al.* references. Specifically, the Weisner *et al.* reference also fails to teach or suggest a genotyping method that requires ***a set of distinguishably labeled downstream amplification primers***, as is required by the claimed invention.

Based on all of the above, Applicant respectfully submits that none of the cited references of Myakishev *et al.*, Nolan *et al.*, and Weisner *et al.*, alone or in combination, teaches or suggests a genotyping method comprising, among other elements, subjecting to an amplification regimen a population of primer extension products generated from a nucleic acid sample, wherein said amplification regimen is performed using an upstream amplification primer and ***a set of distinguishably labeled downstream amplification primers***, as is presently claimed.

Accordingly, Myakishev *et al.*, Nolan *et al.*, and Weisner *et al.* fail to teach or suggest the claimed invention and, thus, Applicants respectfully request reconsideration and withdrawal of the above rejections of claims 55, 56, 67 and 68 under 35 U.S.C. §103(a).

SUMMARY

In view of the foregoing, applicant requests reconsideration, withdrawal of all rejections, and allowance of all the pending claims in due course. If a telephone conversation with Applicant's undersigned representative would move this application to allowance faster, the Examiner is urged to call (617) 439-4444.

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Respectfully submitted,

By _____

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